





Preeclampsia & kidney

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Happy family





Healthy Pregnancy

Physiological process with possible serious complications

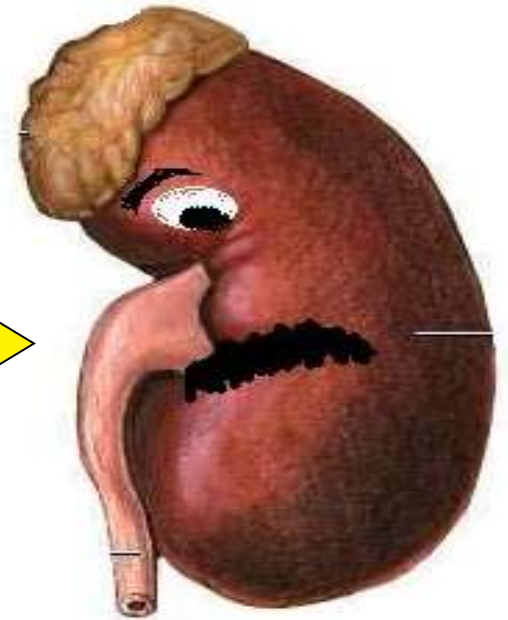
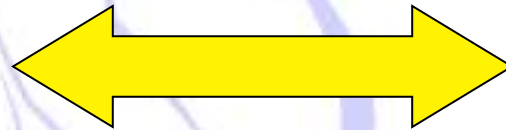


The Whole Family Suffers



Preeclampsia and kidney

preeclampsia



The Glomerular Injury of Preeclampsia

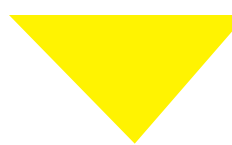
Isaac E. Stillman^{*†} and S. Ananth Karumanchi^{†‡}

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J Am Soc Nephrol 18: 2281–2284, 2007.



case presentation

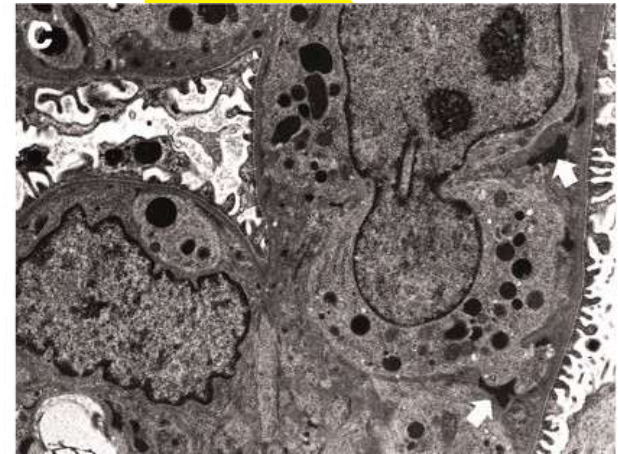
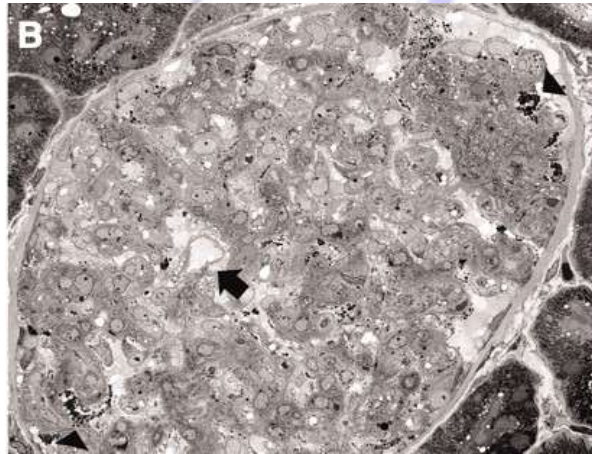
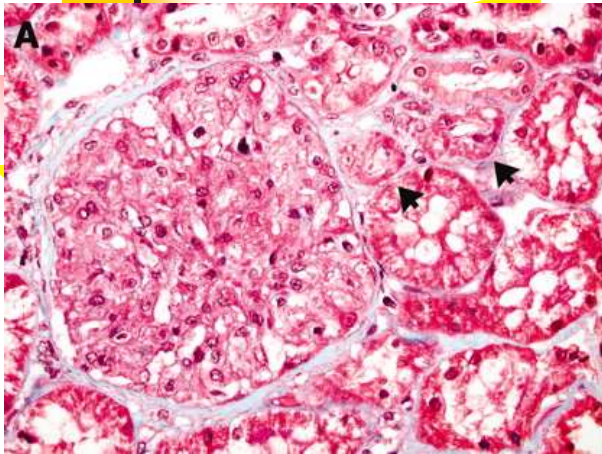
- A 30-yr-old pregnant woman (G1P0), at 15 wk gestation, presented with new-onset hypertension (160/100) and nephrotic-range proteinuria (3gm/24 h).
 - Her medical history was significant for polycystic ovary syndrome.
- 



Case presentation

- This pregnancy was the result of *in vitro fertilization*, which was followed by fetal reduction, leaving her with **twins**.
- Her **hypertension** was unresponsive to medication , and she was admitted to the hospital for treatment.
- **Complement** levels were normal, and **serologic** workup, was negative.

Renal biopsy



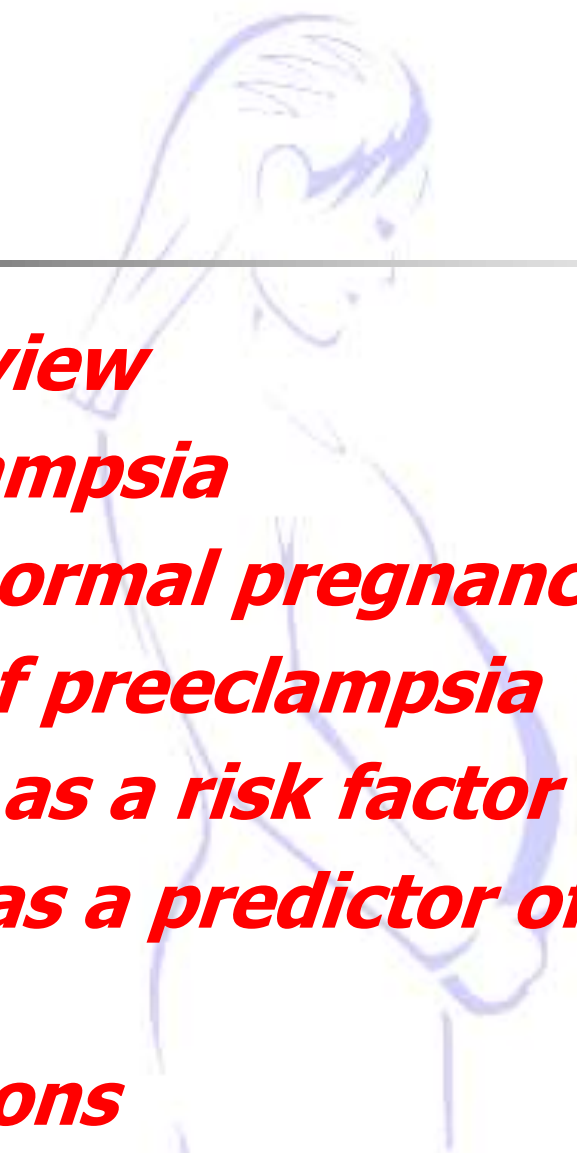
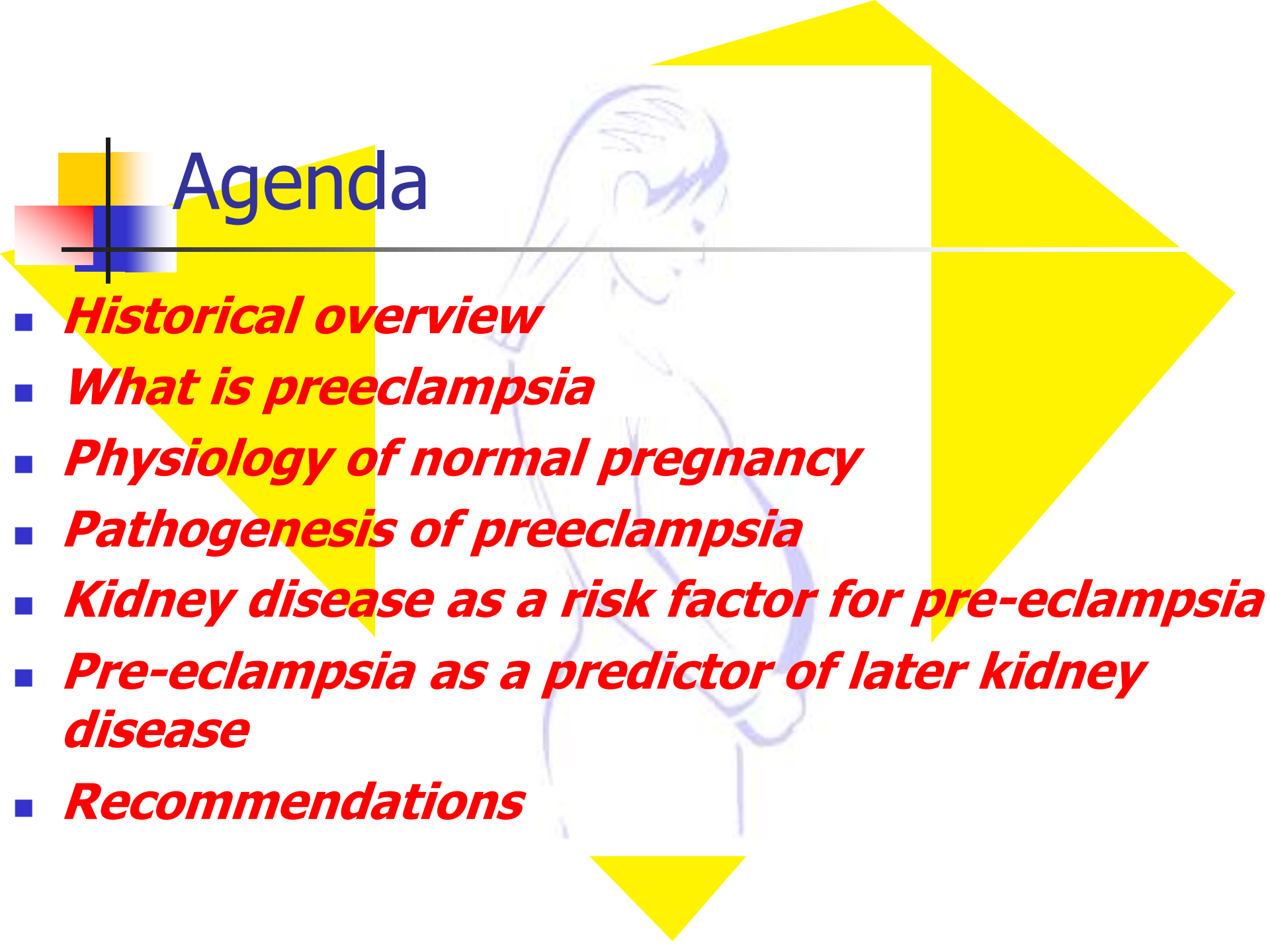
What is this pathology?
What is the pathogenesis?

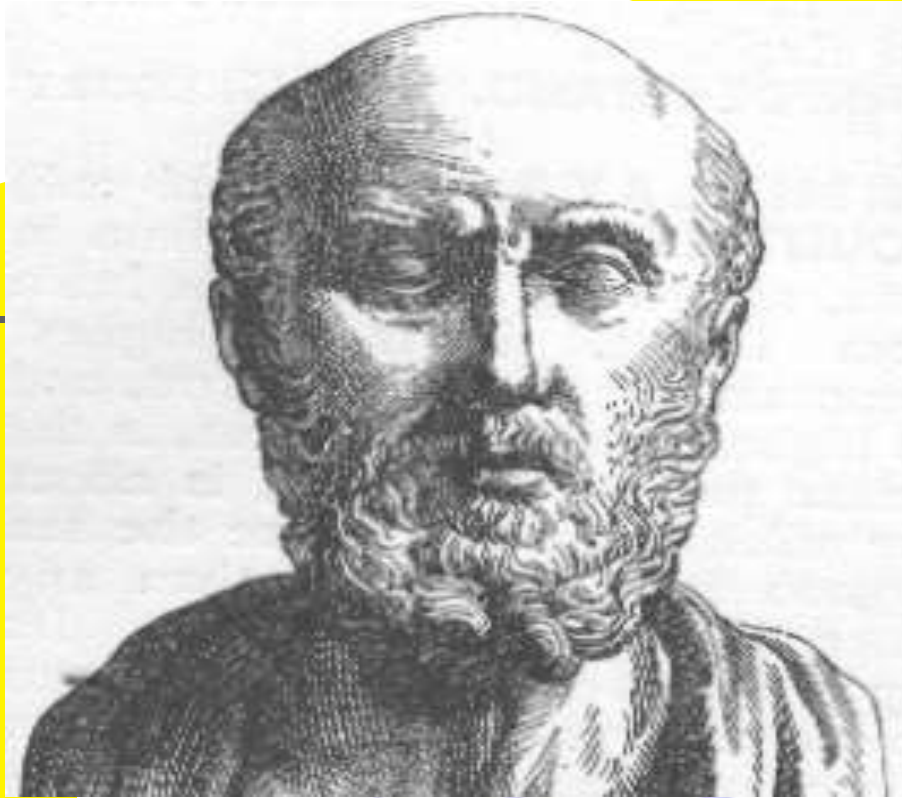
What about its fate & future risk?

What is our role in the management of such cases?



Agenda

- ***Historical overview***
 - ***What is preeclampsia***
 - ***Physiology of normal pregnancy***
 - ***Pathogenesis of preeclampsia***
 - ***Kidney disease as a risk factor for pre-eclampsia***
 - ***Pre-eclampsia as a predictor of later kidney disease***
 - ***Recommendations***
- 
- 

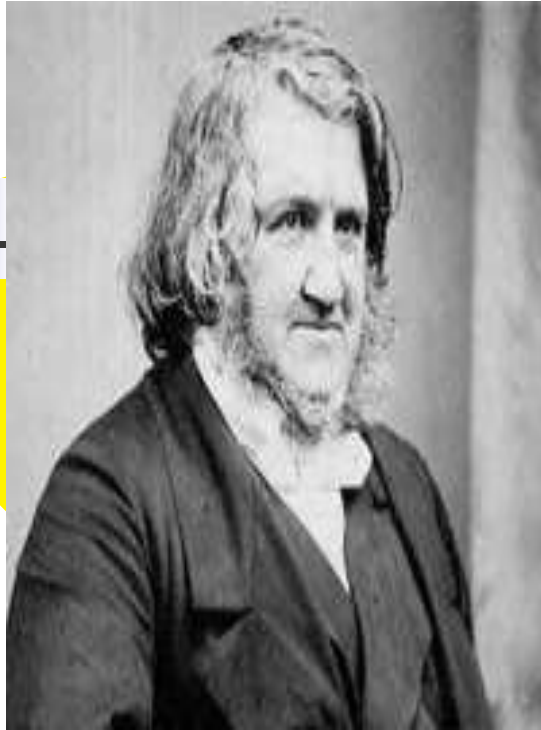


HIPPOCRATES 16TH CENTURY

"headache accompanied by heaviness
and
convulsions during pregnancy was
considered bad."



first to use the term, "**eclampsia**", a Greek word meaning "**lightning**", perhaps it refers to a **sudden** and **unexpected convulsions** that may arise in the pregnant ladies.



**John Lever
(1811-1859)**

First who
demonstrated that
the **proteinuria**
accompanying
eclampsia was
specific
to that disease, and
not part of a general
disorder



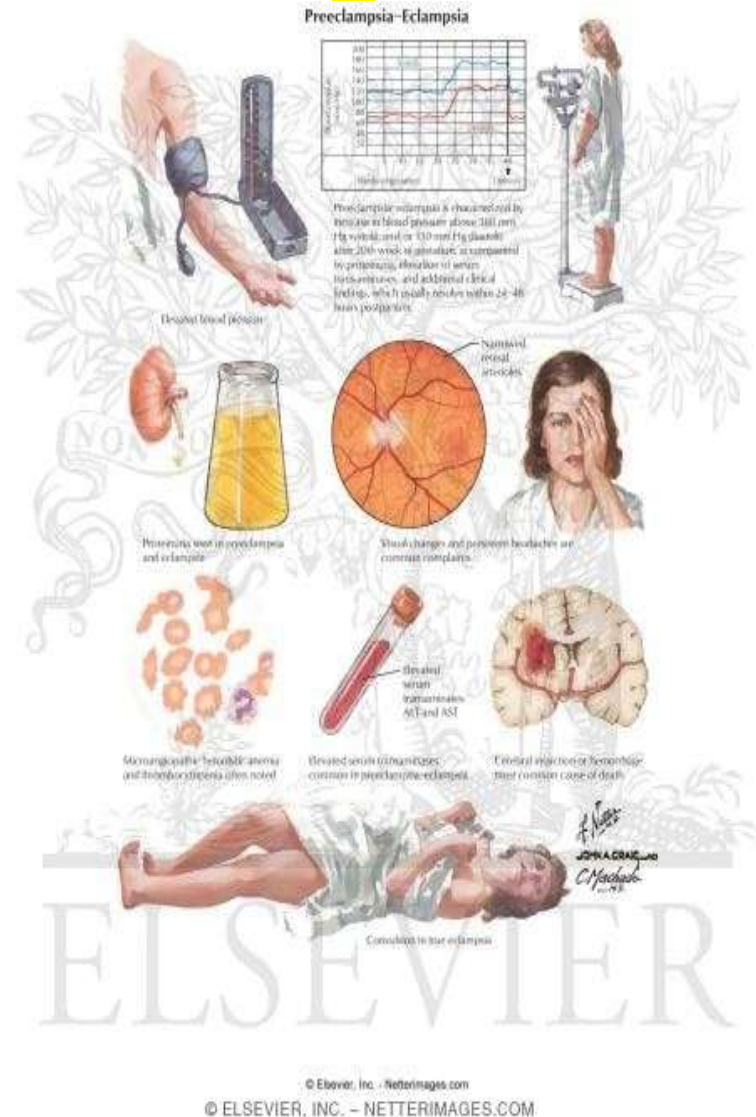
**Scipione
Riva-Rocci(1863-
1947)**

Scipione
Riva-Rocci's **mercury
manometer** (1896) to
measure blood pressure
that led to the recognition
that **preeclampsia was a •
hypertensive disorder;**

from then until now, **new •
onset of hypertension
and proteinuria** have been
the major signs used to
identify preeclampsia

preeclampsia

Preeclampsia (PE) is a pregnancy-specific and multisystemic disorder characterized by the onset of high blood pressure and proteinuria which develop after 20th week of gestation.





preeclampsia

- preeclampsia complicate up to 8% of pregnancies.
- So, It is considered the ??? most common glomerular disease worldwide
- It remains a leading cause of infant and maternal morbidity and mortality.

Physiological review



Renal Changes During Pregnancy



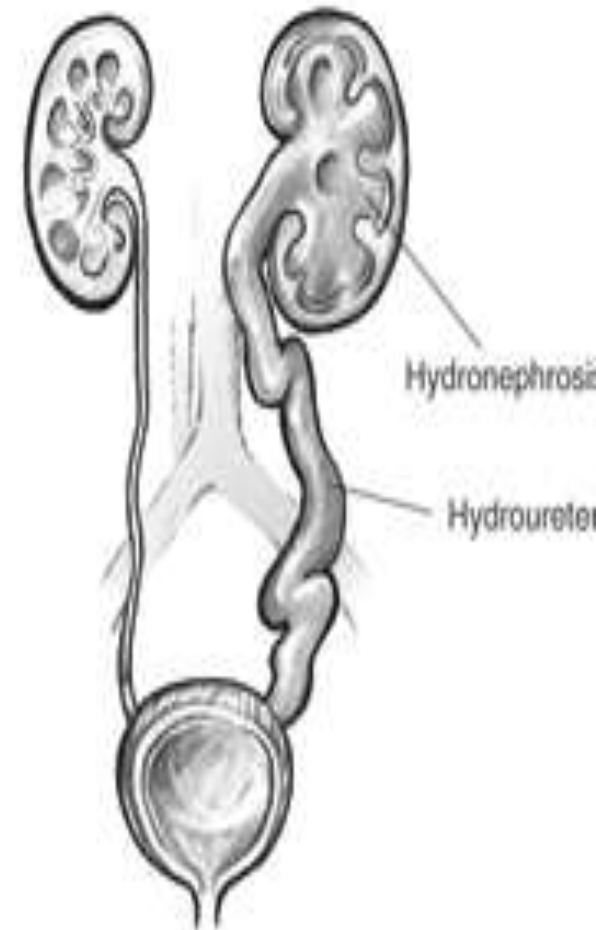
Anatomical changes

Functional Changes

Physiology Review

Dilatation of the collecting system with a small increase in renal size

Anatomical changes



Gynecol Obstet Invest 2012;74:274–281

Physiology Review

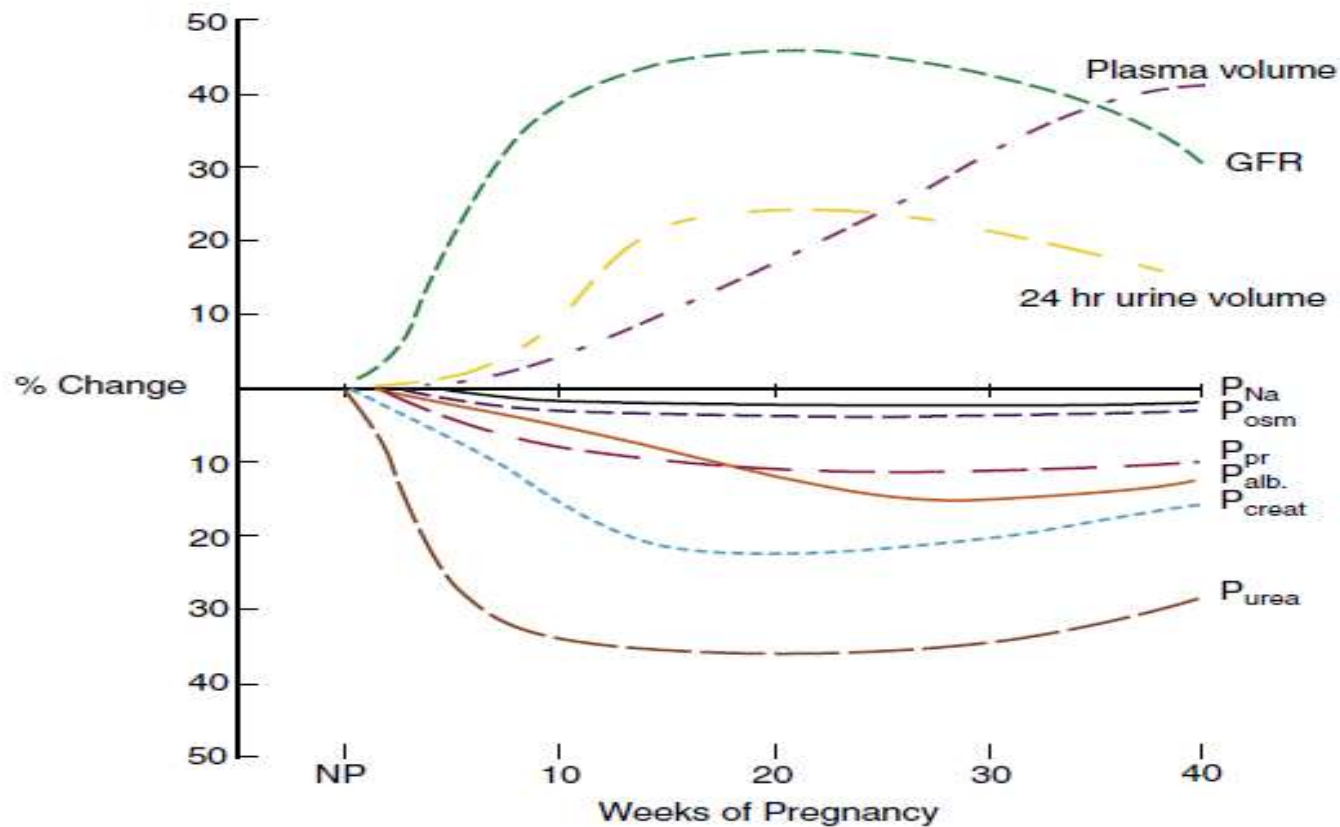
Haemodynamic and glomerular filtration changes

- ↓ Systemic vascular resistance
- ↓ Mean arterial pressure
- ↑ COP
- ↑ RPF & GFR
- ↓ plasma osmolality and serum Na

Gynecol Obstet Invest 2012;74:274–281

Functional Changes

Physiologic changes induced in pregnancy



J Royal Soc Med 76:485-500, 1983.

Renal Changes During Pregnancy

Variable	Non Pregnant	Pregnant	Critical V. pregnancy
PL.Cr	0.65+-0.14 mg/dl	0.46+-0.13 mg/dl	>0.80 mg/dl
BUN	13+-3 mg/dl	8.7+-1.5 mg/dl	>14 mg/dl
Urinary protein	<150 mg/24h	<250-300 mg/24h	>300 mg/24h
Plasma urate	4-6 mg/dl	2.5-4 mg/dl	>5.8 mg/dl
Urinary A.A	_____	Up to 2g/24h	> 2g/24h

Functional Changes



Renal Changes During Pregnancy



Clinical Implications

Anatomical changes

Functional Changes



Clinical Implications

Urinary frequency

Incontinence

Nocturia

Dependent edema





Clinical Implications

After Delivery

Anatomical Changes

Functional Changes



After Delivery



- **All changes return to normal**

What is the problem ?

PREECLAMPSIA PATHOGENESIS



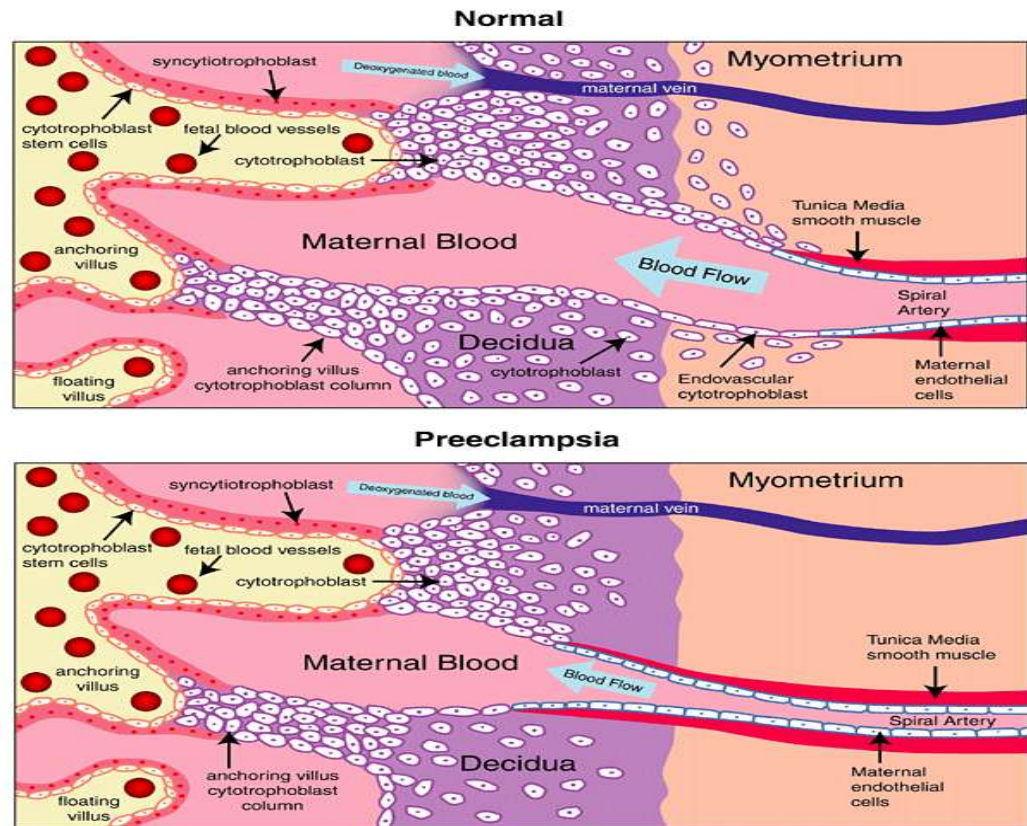
Pathogenesis

- One of the **great mysteries** in the field of OB.
 - Although the understanding of its pathophysiology has been increased over the past 50 years, It is still labeled a **"disease of theories"**.



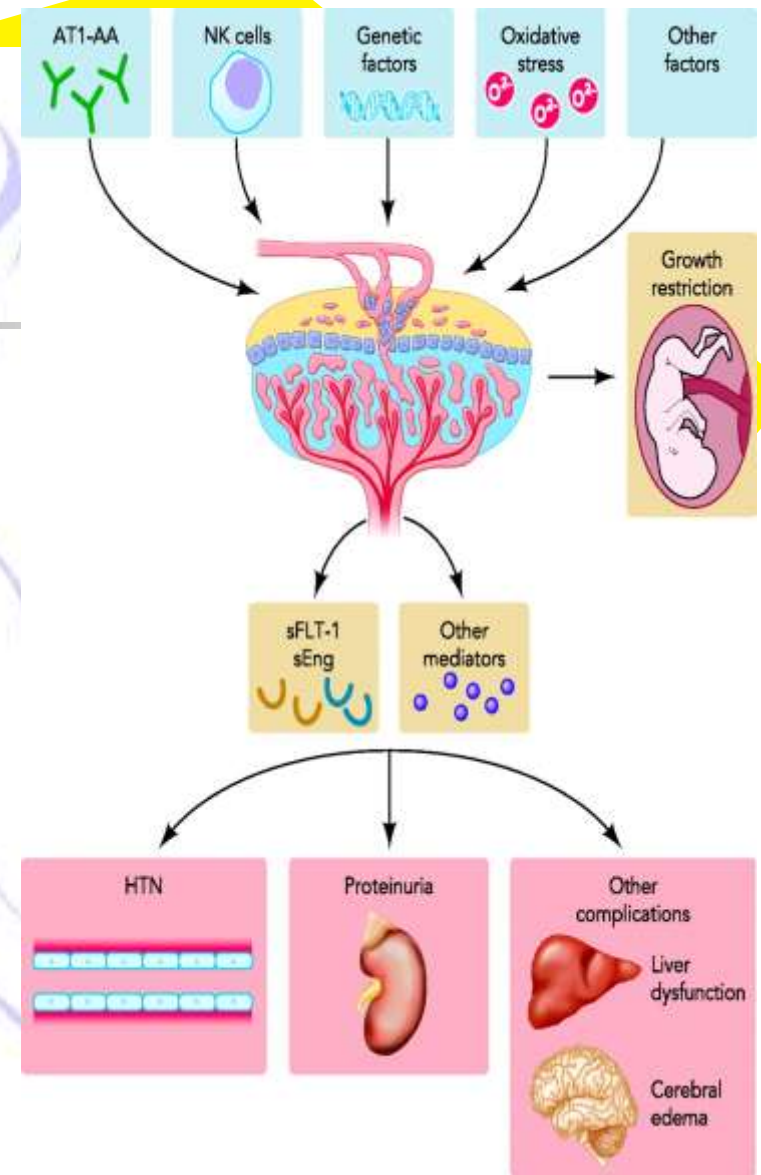
Abnormal placentation

The pathophysiologic changes include disturbances in the vascular development of placenta resulting in **placental hypoperfusion and ischaemia.**

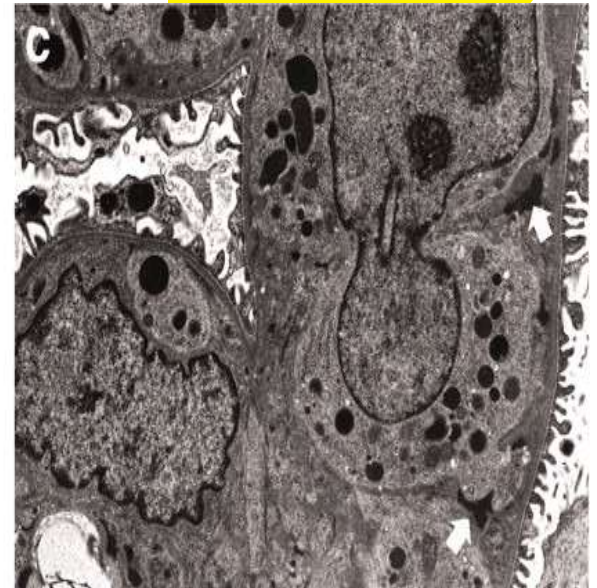
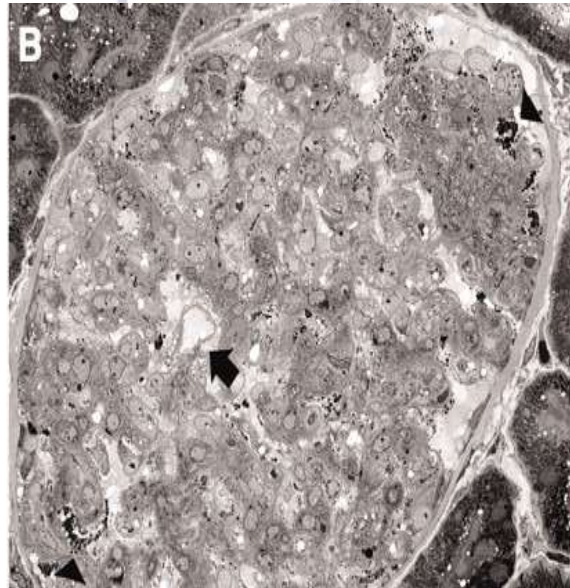
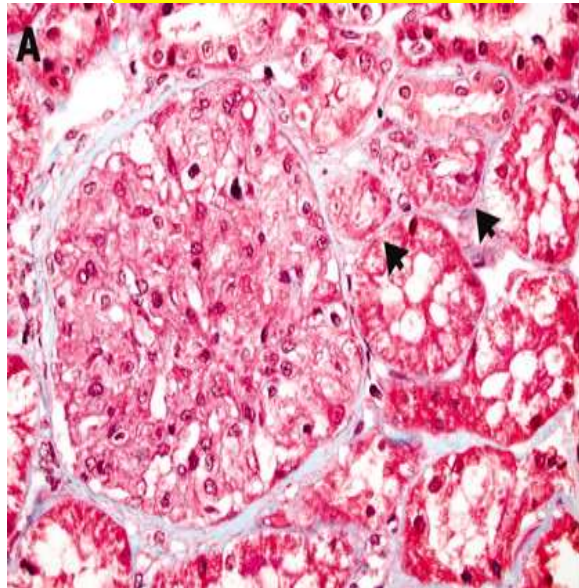


Circulation 2011; 123:2856-2869

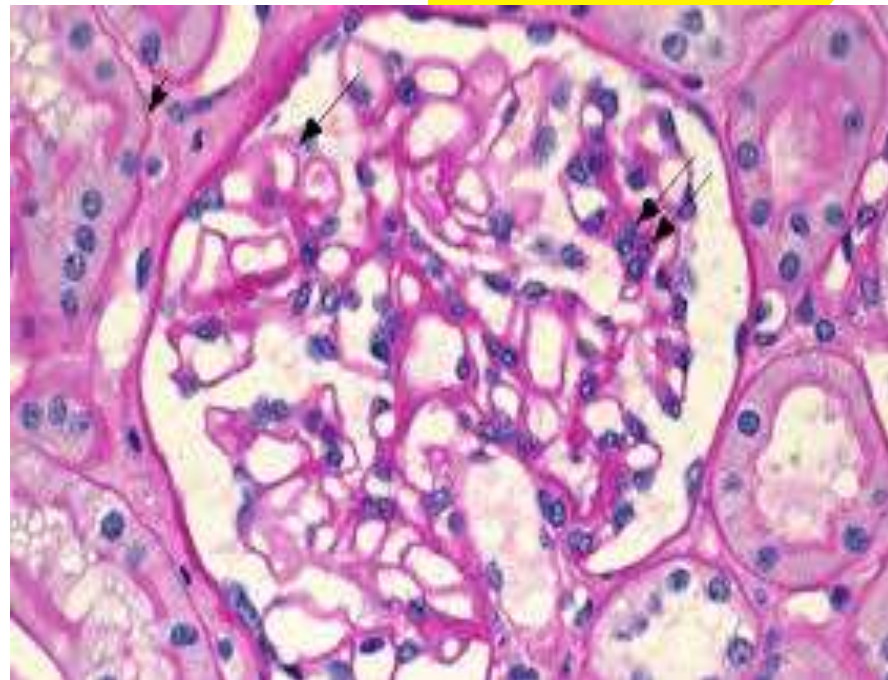
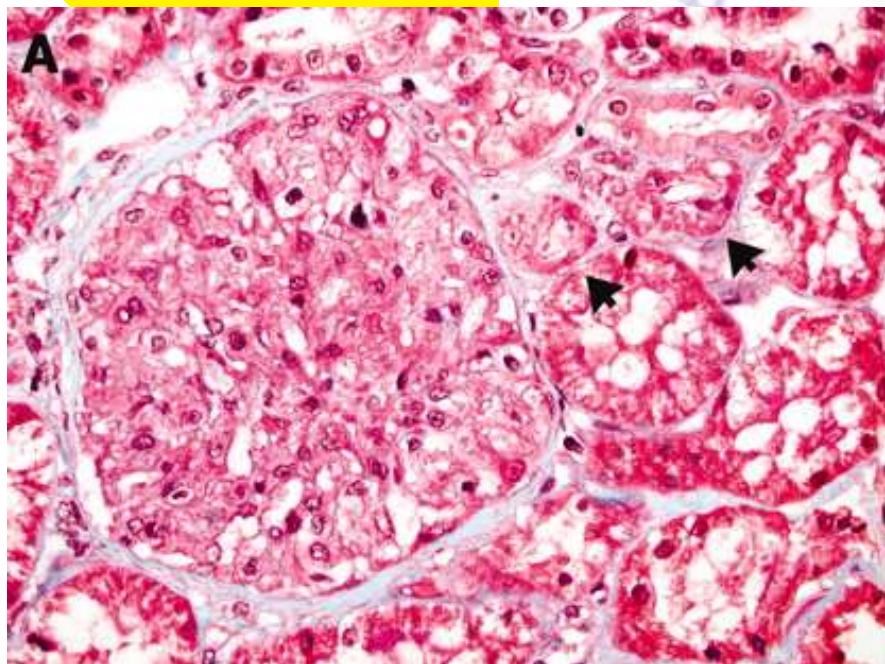
- The damaged placenta, in turn, secretes a wide range of **anti-angiogenic factors** into the maternal circulation that is believed to cause a systemic **endothelial cell dysfunction** and **microangiopathy**



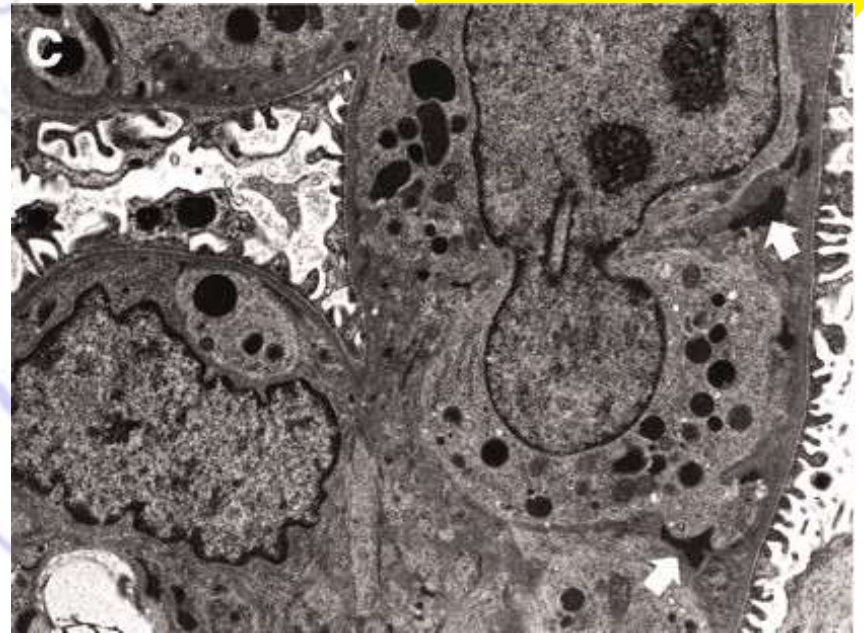
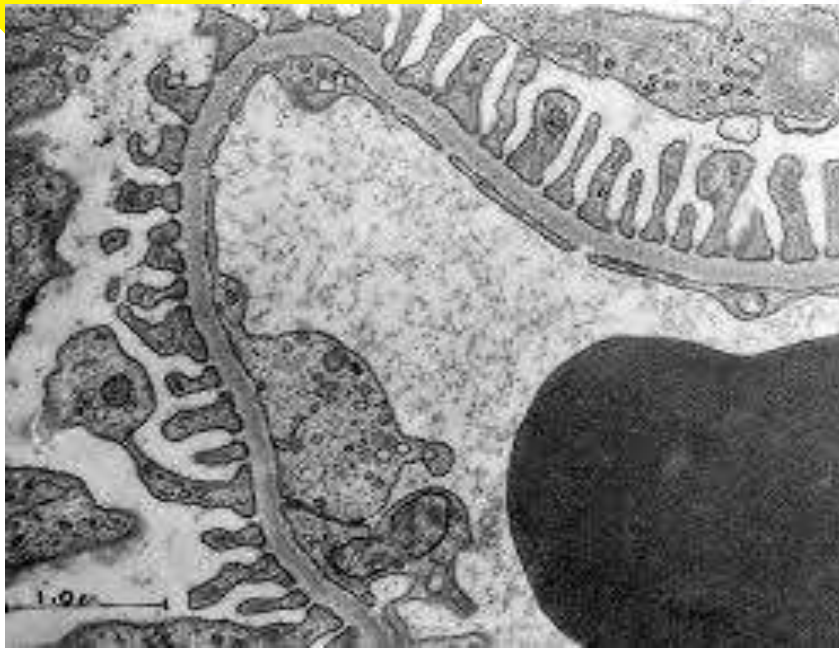




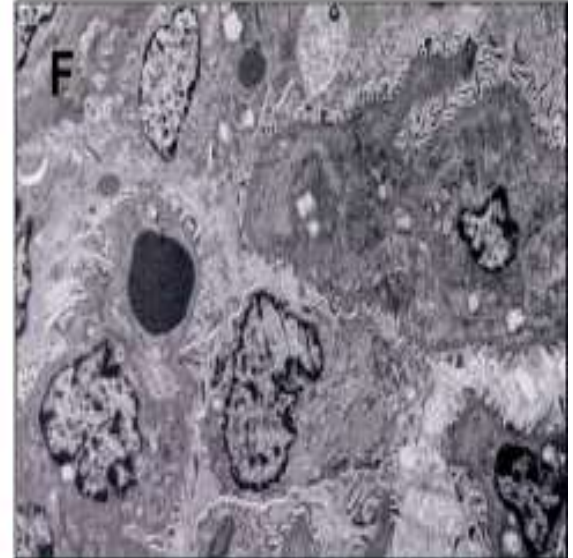
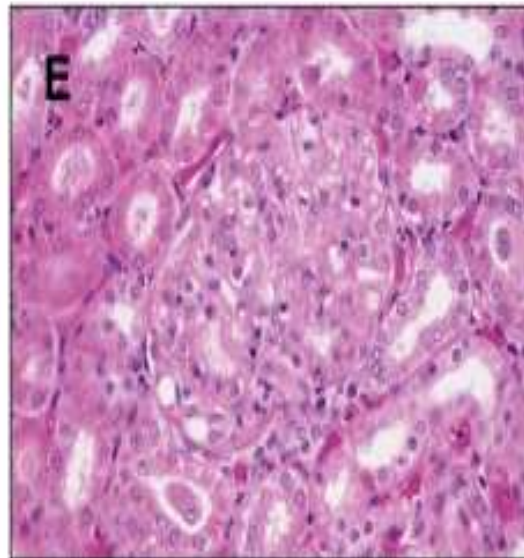
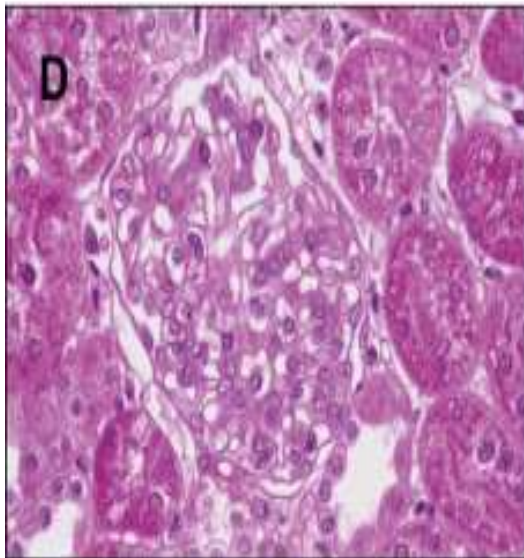
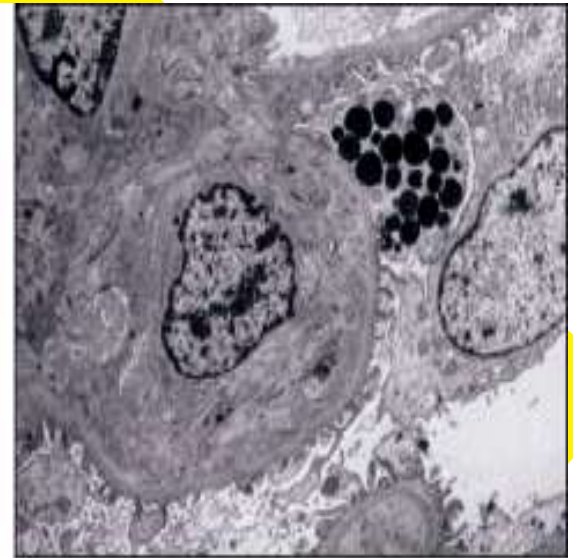
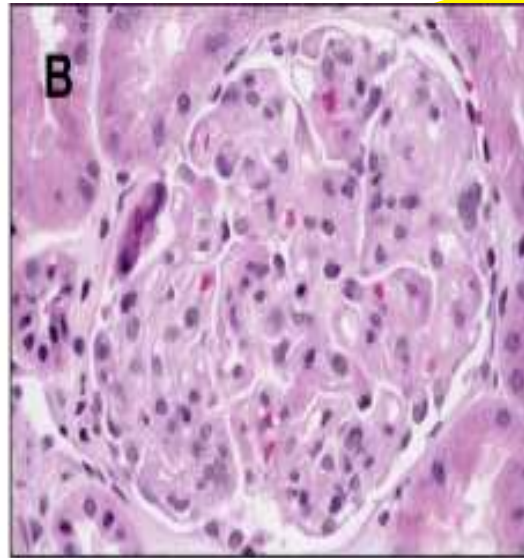
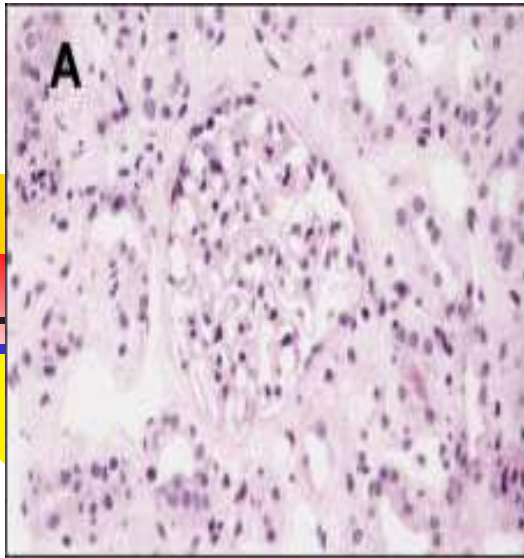
J Am Soc Nephrol 18: 2281–2284, 2007.



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What is Glomerular Endotheliosis?

- The glomeruli are enlarged and solidified (“bloodless”), as a result of **narrowed** or **occluded** capillary lumens that are the result of **swelling** of the native endothelial cells .
Together with deposition of **fibrin** and **fibrinogen** material in and beneath the endothelial cells

J Am Soc Nephrol 18: 2281–2284, 2007.

Renal pathology of preeclampsia

- **Glomerular cellularity** is not significantly increased.
- **Tubules** and **arterioles** are typically unaffected.
- Thrombosis by light microscopy unusual, In marked contrast, in **nonpreeclamptic TMA**, thrombosis of vessels and/or glomeruli is a central finding

Proteinuria and preeclampsia

Mild forms have been seen in up to 30% of patients with pregnancy-induced hypertension without proteinuria (Strevens et al 2003).



Role of podocytes

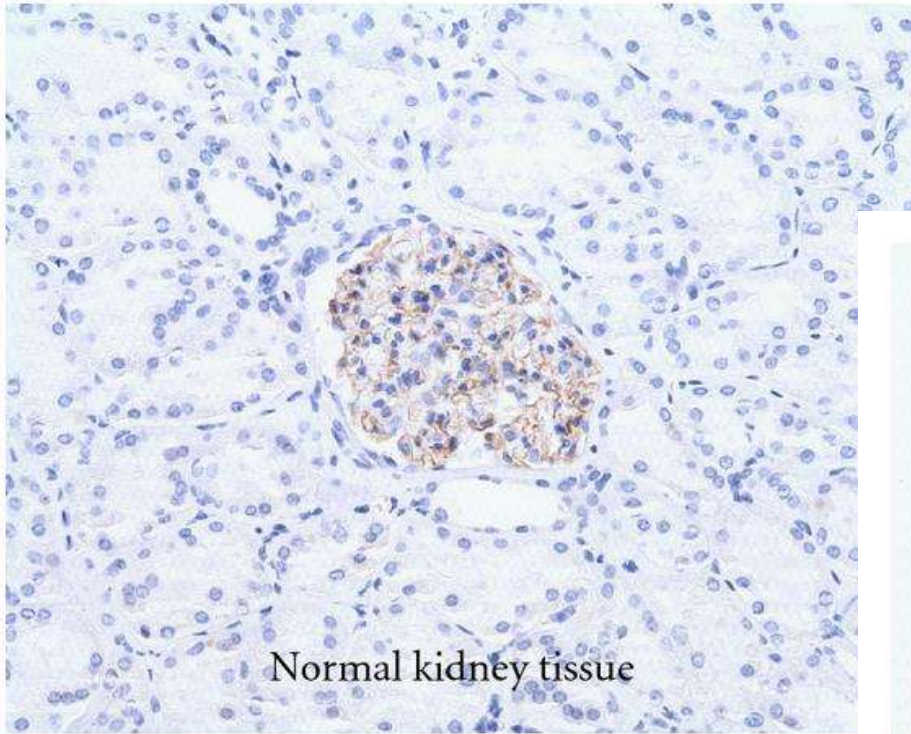
- Podocyte alterations and **podocytopathies** have been described during preeclampsia .
- Disturbances of podocyte biology including **impaired survival, enhanced apoptosis and down-regulation of nephrin, synaptopodin and other key proteins of the slit diaphragm**



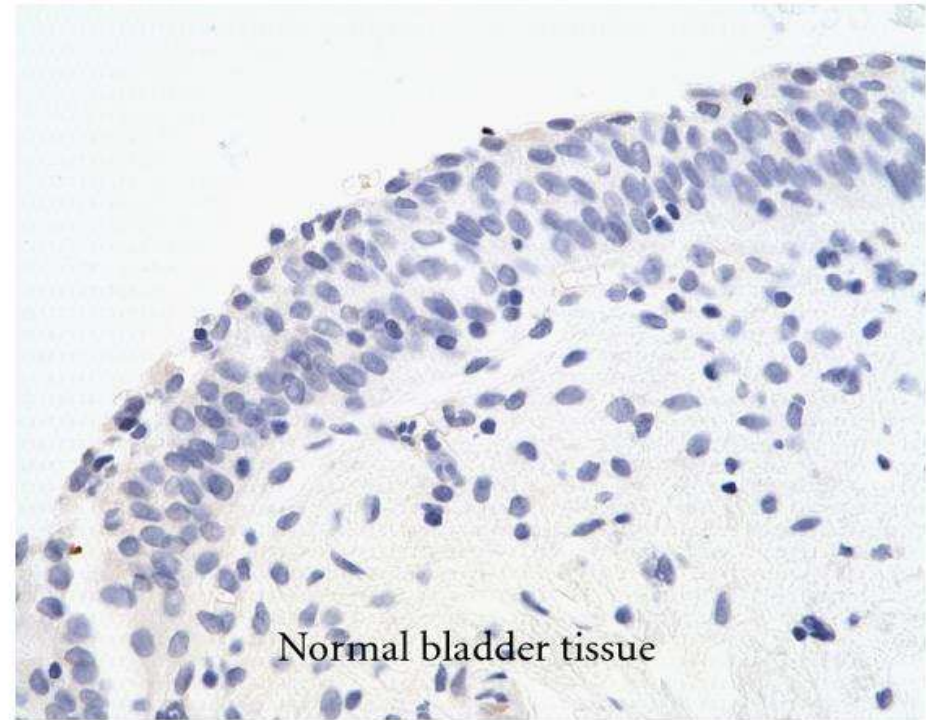
Research Article

Podocyturia as a Diagnostic Marker for Preeclampsia amongst High-Risk Pregnant Patients

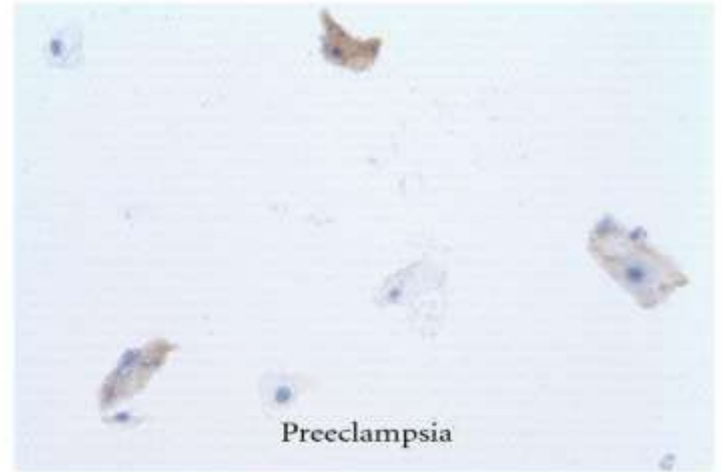
Belinda Jim,¹ Pascale Jean-Louis,^{1,2} Andi Qipo,¹ David Garry,² Samia Mian,³ Tulio Matos,⁴ Christopher Provenzano,¹ and Anjali Acharya¹



Normal kidney tissue



Normal bladder tissue



Test characteristics for podocyturia

	Podocyte positive	Podocyte negative	% Positive
Preeclampsia/eclampsia (29)	11	18	38%
HTN-Gestational/chronic (9)	3	6	33%
DM: any type (6)	3	3	50%
^a Others (3)	2	1	66%
^b Controls (9)	0	9	0%

Podocyturia does not appear to be a sensitive nor a specific marker to diagnose preeclampsia.

^aOther: diagnoses of marginal previa (1), chromosomal anomaly (1), connective tissue disorder (1).

^bControls: uncomplicated pregnancies.



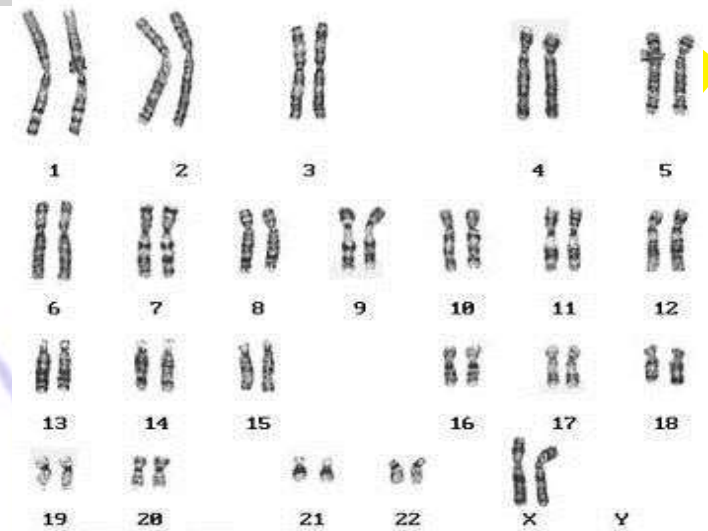


Back to the case

- Attempts to **control her BP** using nifedipine and Aldomet were partially successful.
- Her **proteinuria** continued to rise (peak urine protein/ creatinine ratio **9**).
- After much counseling, the patient, considering the severity of the disease and the relatively early gestational age, elected to **terminate the pregnancy**.

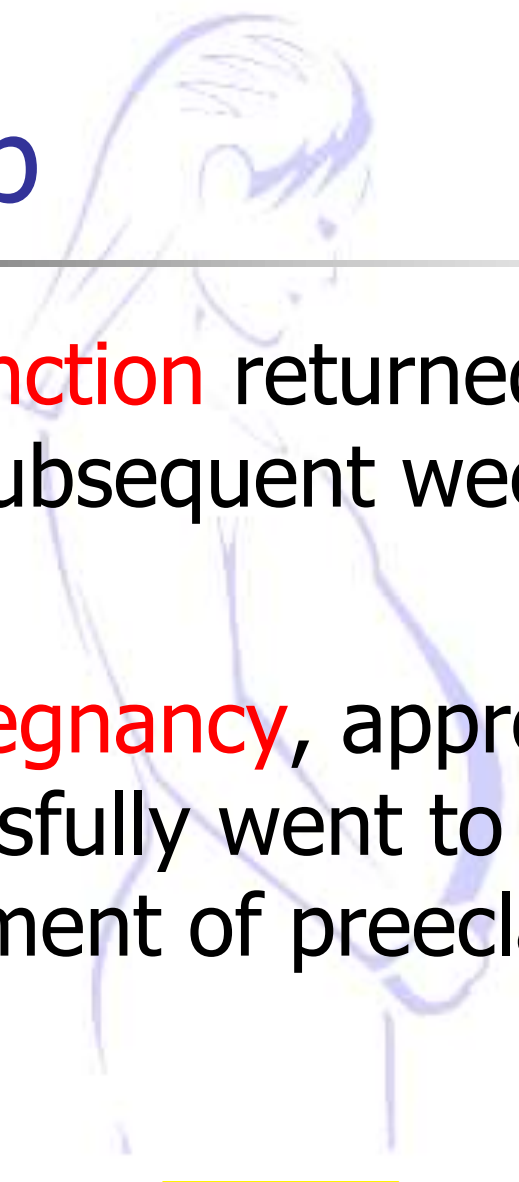
Cytogenetic analysis

- Cytogenetic analysis revealed normal fetuses, and there was no evidence of a molar pregnancy.





Follow Up

- Her **renal function** returned to normal during the subsequent weeks
 - A **second pregnancy**, approximately 2 yr later, successfully went to term without the development of preeclampsia.
- 



kidney

- Is kidney disease a risk factor for pre-eclampsia?

Preeclampsia

- Does Pre-eclampsia predict a later kidney disease?

PREGNANCY IN CKD patients

- Pregnancy is relatively uncommon and prevalence estimates range from 0.03% to 0.12%

- Early pregnancy losses occur frequently

- The majority who become pregnant bring forth surviving infants,
- The risk for pre-eclampsia and other pregnancy complications is increased

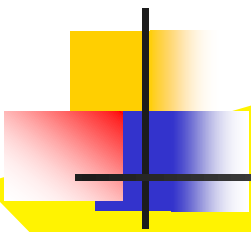
Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

Persistent albuminuria categories Description and range		
A1	A2	A3
Normal to mildly increased	Moderately increased	Severely increased
<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol

GFR categories (mL/min/1.73 m ²) Description and range	G1	Normal or high	≥90	Green	Yellow	Orange
	G2	Mildly decreased	60-89	Green	Yellow	Orange
	G3a	Mildly to moderately decreased	45-59	Yellow	Orange	Red
	G3b	Moderately to severely decreased	30-44	Orange	Red	Red
	G4	Severely decreased	15-29	Red	Red	Red
	G5	Kidney failure	<15	Red	Red	Red

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.



Cunningham *et al.* evaluated **37** pregnancies in women with moderate to severe renal insufficiency and reported pre-eclampsia in **58%** and **64%** of the pregnancies, respectively.

Am J Obstet Gynecol 1990; 163: 453–459

Superimposed Preeclampsia in Women with Chronic Kidney Disease

Abstract

Hisashi Ma:
Tomonori S

Department of
Pharmaceutical

Aim: To evaluate whether pregnant women with chronic kidney disease (CKD) adapt poorly to increases in renal blood flow. This can exacerbate renal function and impair perinatal outcome, as there is a major interplay between CKD and preeclampsia (PE). **Methods:** We analyzed the outcomes of 90

Conclusion: *Pregnancies with CKD have*

a high risk of obstetrical complications. Angiogenic factors might be potential markers for a differential diagnosis between PE and worsening renal function

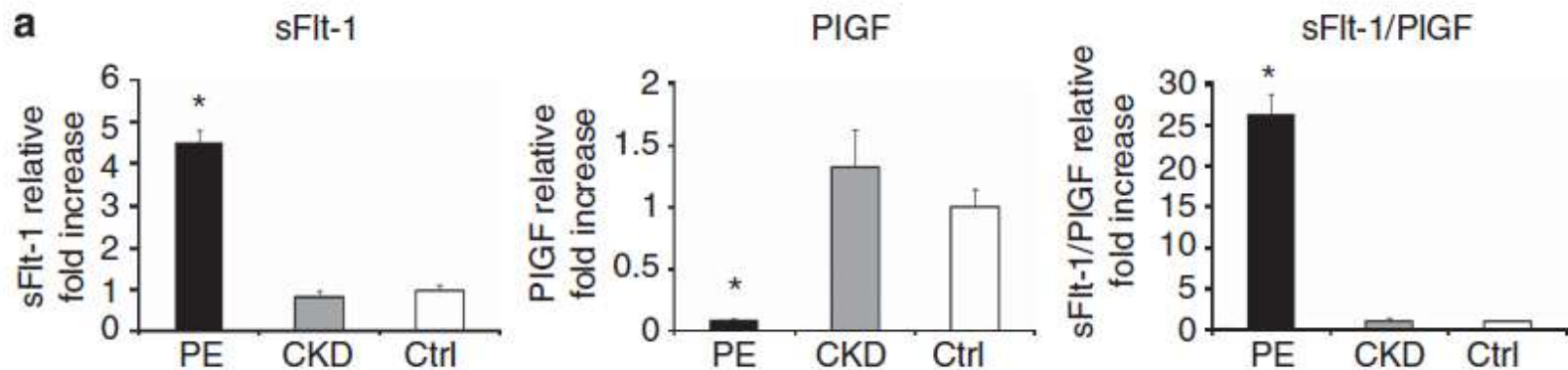
pregnant women with preexisting CKD. The estimated glomerular filtration rate (eGFR) was measured along with the level of angiogenic factors, soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor, which might affect in the pathophysiology of PE. **Results:** In pregnancies with CKD, PE and preeclampsia (PE) were increased and the increased blood pressure worsened the perinatal outcomes much more than the increased proteinuria. All pregnancies with severe renal insufficiency were delivered preterm because of impaired renal function. The eGFR was correlated signifi-

Chronic kidney disease may be differentially diagnosed from preeclampsia by serum biomarkers

Alessandro Rolfo¹, Rossella Attini¹, Anna M. Nuzzo¹, Annalisa Piazzese¹, Silvia Parisi¹, Martina Ferraresi², Tullia Todros¹ and Giorgina B. Piccoli²

¹Department of Obstetrics and Gynecology, O.I.R.M.-Sant'Anna Hospital, University of Turin, Turin, Italy and ²SS Nephrology, Department of Biological and Clinical Sciences, University San Luigi – Orbassano, Turin, Italy

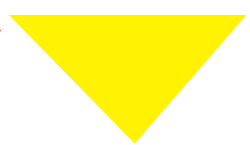
They tested whether maternal serum levels of placental growth factor (PIGF) and soluble FMS-like tyrosine kinase-1 (sFlt-1), markers of preeclampsia, could be used to discriminate between 34 patients with preeclampsia 23 patients with CKD during pregnancy, and 38 healthy pregnant women.





.....Why to discriminate

Early diagnosis of superimposed PE might improve clinical outcomes

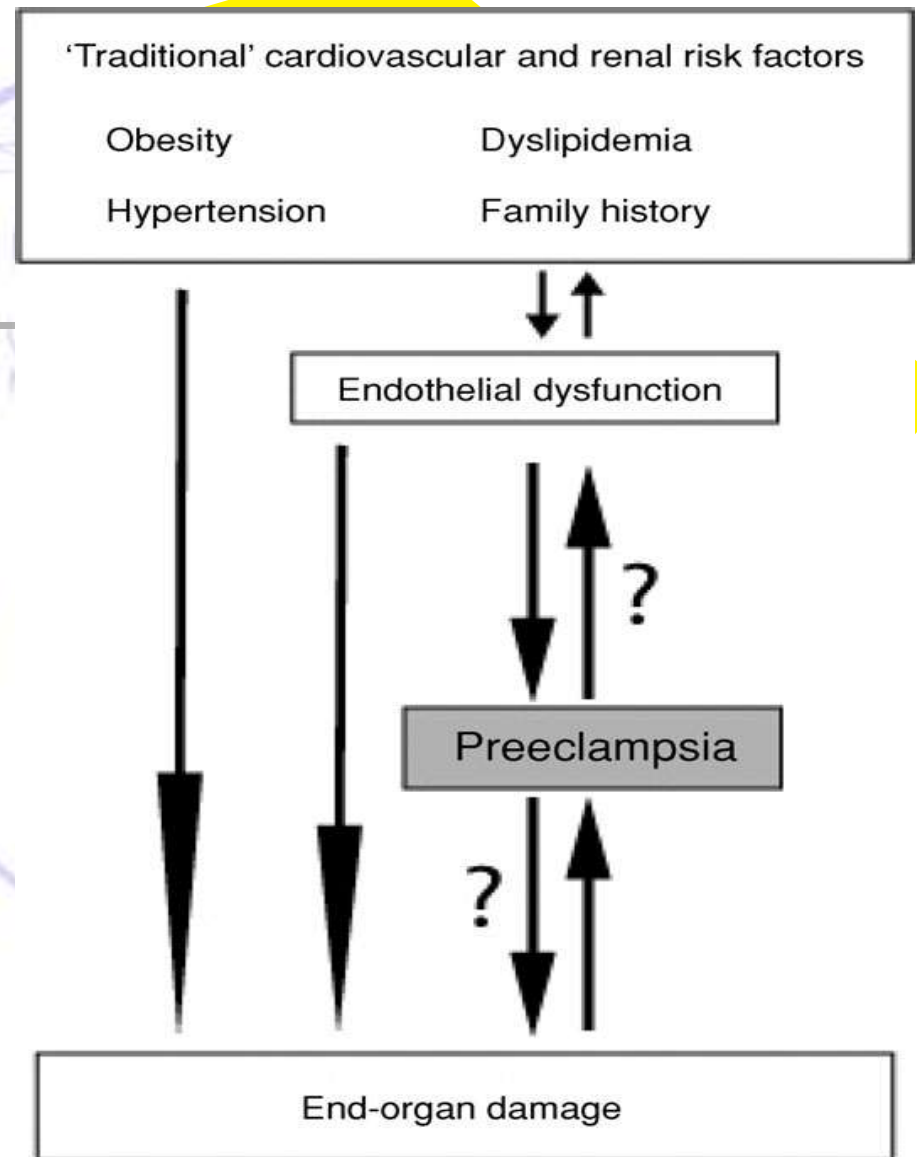
- intensive monitoring
 - antihypertensive medications,
 - bed rest,
 - magnesium for seizure prophylaxis,
 - steroids for fetal lung maturity and
 - expedient delivery
- 



Does Pre-eclampsia
predict a later
kidney disease?

CKD

Pre-eclampsia may be an intermediate factor in the development of end-organ damage.



Preeclampsia and the Risk of End-Stage Renal Disease

Bjørn Egil Vikse, M.D., Ph.D., Lorentz M. Irgens, M.D., Ph.D.,
Torbjørn Leivestad, M.D., Ph.D., Rolv Skjærven, Ph.D.,
and Bjarne M. Iversen, M.D., Ph.D.

ABSTRACT

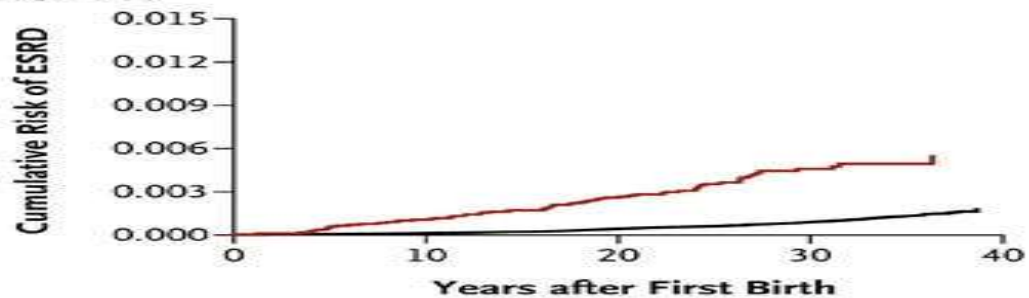
BACKGROUND

It is unknown whether preeclampsia is a risk marker for subsequent end-stage renal disease (ESRD).

METHODS

We linked data from the Medical Birth Registry of Norway, which contains data on all births in Norway since 1967, with data from the Norwegian Renal Registry, which contains data on all patients receiving a diagnosis of end-stage renal disease (ESRD) since 1980, to assess the association between preeclampsia in one or more pregnancies and the subsequent development of ESRD. The study population consisted of women who had had a first singleton birth between 1967 and 1991; we included data from up to three pregnancies.

A After One Pregnancy



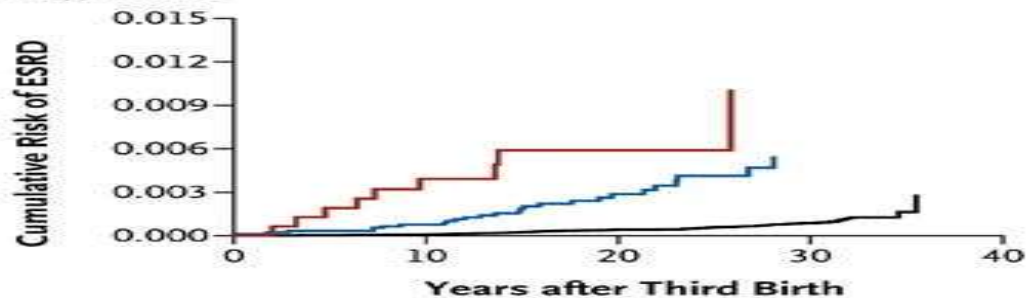
— Preeclampsia

No. at risk	11,511	18,565	12,048	4288	0
No. with ESRD	0	16	44	64	67

— No Preeclampsia

No. at risk	252,572	477,847	341,327	142,775	0
No. with ESRD	0	42	190	327	410

C After Three Pregnancies



— Preeclampsia in Two or More Pregnancies

No. at risk	1498	1359	516	102	0
No. with ESRD	0	6	8	9	9

— Preeclampsia in One Pregnancy

No. at risk	8708	8638	4020	974	0
No. with ESRD	0	7	20	26	26

— No Preeclampsia

No. at risk	151,346	166,165	86,389	23,000	0
No. with ESRD	0	14	56	76	84

NEJM 2008 Aug 21;359(8):800-9

ORIGINAL ARTICLE

Preeclampsia and the Risk of End-Stage Renal Disease

Bjørn Egil Vikse, M.D., Ph.D., Lorentz M. Irgens, M.D., Ph.D.,
Torbjørn Leivestad, M.D., Ph.D., Rolv Skjærven, Ph.D.,
and Bjarne M. Iversen, M.D., Ph.D.

preeclampsia is a clinical marker for an increased risk of subsequent ESRD. The risk is greater if preeclampsia occurs in more than one pregnancy

NEJM 2008 Aug 21;359(8):800-9

Association between hypertensive disorders during pregnancy and end-stage renal disease: a population-based study

I-Kuan Wang MD, Chih-Hsin Muo MS, Yi-Chih Chang PhD, Chih-Chia Liang MD, Chiz-Tzung Chang MD PhD, Shih-Yi Lin MD, Tzung-Hai Yen MD PhD, Feng-Rong Chuang MD, Pei-Chun Chen PhD, Chiu-Ching Huang MD, Chi-Pang Wen MD PhD, Fung-Chang Sung PhD, Donald E. Morisky ScD

See related commentary by Spaan and Brown on page 199 and at www.cmaj.ca/lookup/doi/10.1503/cmaj.130007

ABSTRACT

Background: Studies into the association between hypertensive disorders during pregnancy and end-stage renal disease are limited. We investigated the risk of end-stage renal disease after delivery among women with hypertensive disorders during pregnancy.

Methods: We used insurance claims data from 1998 to 2009 to identify 26 651 women aged 19–40 years old who experienced hypertensive disorders during pregnancy; these women had no history of hypertension, diabetes, kidney disease or lupus. We also randomly selected 213 397 women without hypertensive disorders during pregnancy as a comparison cohort; the frequency was matched by age and index year of pregnancy. We compared the incidence of end-stage renal disease in the 2 cohorts. We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) after controlling for demographic and clinical factors.

Results: Women with hypertensive disorders during pregnancy had a greater risk of chronic kidney disease and end-stage renal disease, with adjusted HRs of 9.38 (95% CI 7.09–12.4) and 12.4 (95% CI 8.54–18.0), respectively, after controlling for urban status, coronary artery disease, congestive heart failure, hyperlipidemia and abortion. The HR for end-stage renal disease was 2.72 (95% CI 1.76–4.22) after we also controlled for hypertension and diabetes. Women with preeclampsia or eclampsia had a higher risk of end-stage renal disease (adjusted HR 14.0, 95% CI 9.43–20.7) than women who had gestational hypertension only (adjusted HR 9.03, 95% CI 5.20–15.7).

Interpretation: Women with hypertensive disorders during pregnancy were at a high risk of end-stage renal disease. The risk was much greater for women who had preeclampsia or eclampsia than those who had gestational hypertension only.

Competing interests: None declared.

This article has been peer reviewed.

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CMAJ 2013; DOI:10.1503/cmaj.120230

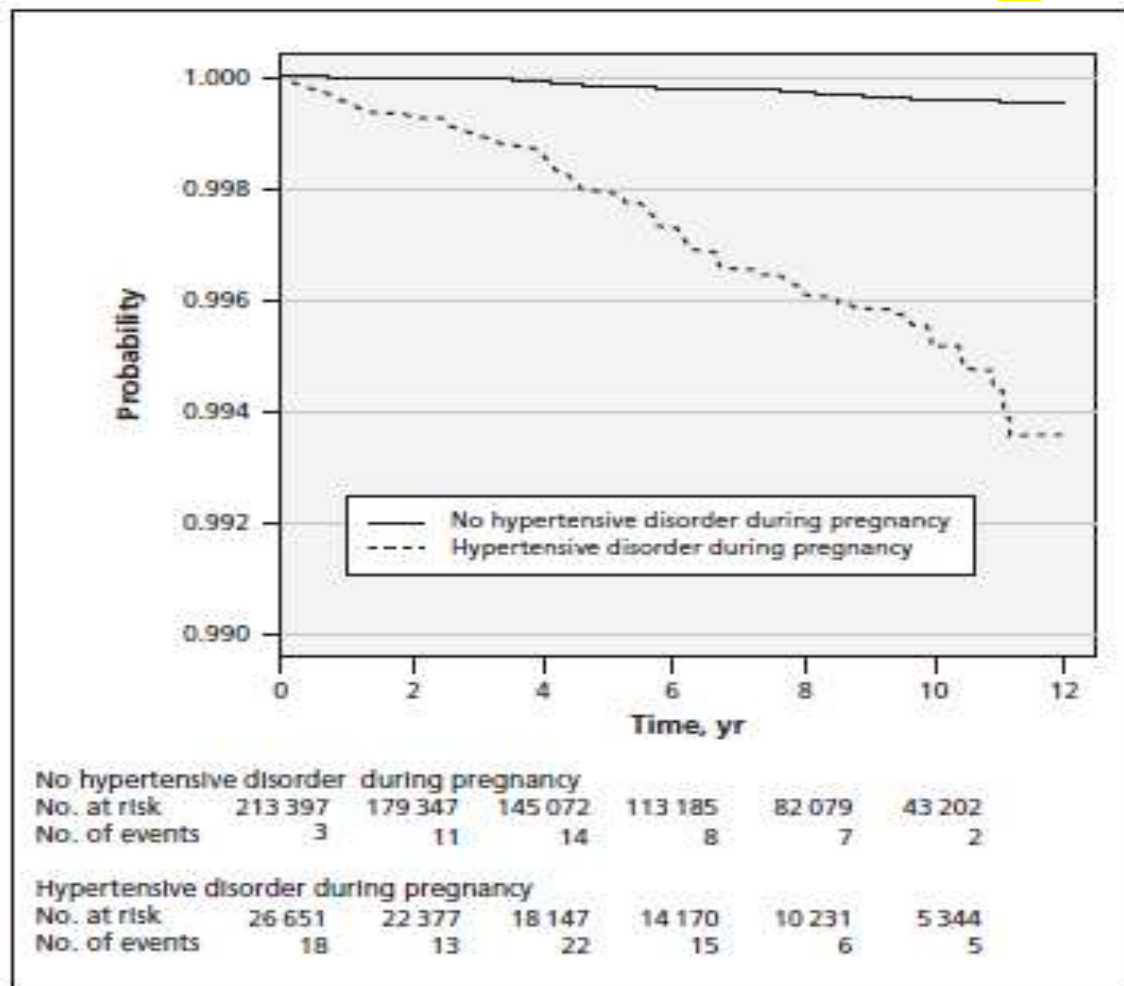
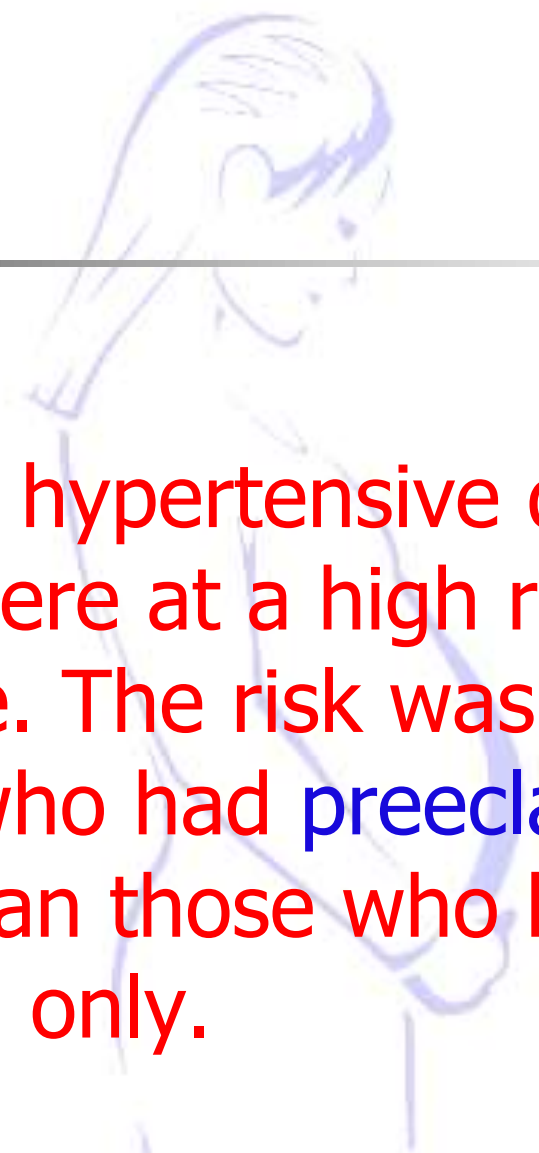


Figure 1: Estimated proportion of women without end-stage renal disease among those with and without hypertensive disorders during pregnancy. Log-rank test, $p < 0.001$.



conclusion:

Women with hypertensive disorders during pregnancy were at a high risk of end-stage renal disease. The risk was much greater for women who had preeclampsia or eclampsia than those who had gestational hypertension only.



Hypothesis

preeclampsia and ESRD share the same factors.

Obesity, hypertension, insulin resistance, and endothelial dysfunction

Microalbuminuria

20 to 40% of women with preeclampsia have microalbuminuria 3 to 5 years after pregnancy, as compared with only 2% of women without preeclampsia

Antiangiogenic factors have been suggested to have an important role in the pathogenesis of preeclampsia and in the progression of chronic renal disorders

preeclampsia may exacerbate subclinical kidney disease that is present before pregnancy

Preeclampsia and the Risk of End-Stage kidney disease

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Persistent Urinary Podocyte Loss following Preeclampsia May Reflect Subclinical Renal Injury

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Abstract

Objective: Studies have shown that podocyturia, i.e., urinary loss of viable podocytes (glomerular epithelial cells), is associated with proteinuria in preeclampsia. We postulated that urinary podocyte loss may persist after preeclamptic pregnancies, thus resulting in renal injury. This may lead to future chronic renal injury. In addition, we compared the postpartum levels of the angiogenic factors, which previously have been associated with preeclampsia, between normotensive versus preeclamptic pregnancies.

Study Design: The diagnosis of preeclampsia was confirmed using standard clinical criteria. Random blood and urine samples were obtained within 24 hours prior to delivery and 5 to 8 weeks postpartum. Urine sediments were cultured for 24 hours to select for viable cells and staining for podocin was used to identify podocytes. Serum samples were analyzed for the levels of angiogenic markers using ELISA (enzyme-linked immunosorbent assay) methodology.

Results: At delivery, preeclamptic patients (n = 10) had significantly higher proteinuria (p = 0.006) and podocyturia (p < 0.001) than normotensive pregnant patients (n = 18). Postpartum proteinuria was similar between these two groups (p = 0.37), while podocyturia was present in 3 of 10 women with preeclampsia and in none of the normotensive controls (p = 0.037). Angiogenic marker levels, including placental growth factor, soluble vascular endothelial growth factor receptor fms-like tyrosine kinase receptor-1 and endoglin, were not significantly different between women with preeclampsia and women with a normotensive pregnancy, either at delivery or postpartum.

Conclusion: Persistent urinary podocyte loss after preeclamptic pregnancies may constitute a marker of ongoing, subclinical renal injury.



Responsibility

Can we protect the kidneys after hypertensive pregnancy?

Julia J. Spaan MD PhD, Mark A. Brown MD

KEY POINTS

- There is an increased risk of end-stage renal disease among women with a history of preeclampsia; those with the more benign disorder of gestational hypertension alone are also at increased risk.
- The development of hypertension, diabetes or both after pregnancy is an important mediator of chronic kidney disease.
- Blood pressure should be monitored regularly after a hypertensive disorder during pregnancy.
- Cardiovascular risk management in a structured multidisciplinary approach may reduce cardiovascular and renal disease after a hypertensive disorder during pregnancy.

recommendations



all women with a history of pre-eclampsia should be **assessed** for a possible primary renal or urinary tract disease.

The focus should be **hypertension, obesity, microalbuminuria** and cardiovascular risk profile

recommendations



Early **lifestyle** intervention and/or
pharmacological treatment
of hypertension and microalbuminuria

Better surveillance after
pregnancy could prevent chronic
kidney disease



Thank you

